IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Philip C. Comp

Serial No.: 08/323,060 Group Art Unit: 1806

Filed: October 14, 1994 Examiner: R. Schwadron

For: Blockage of Protein C Activation Reduces Microvascular Surgical Blood Loss

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132
OF DR. DAVID N. FASS

Sir:

I, Dr. David N. Fass, hereby declare that:

1. I am a researcher in the Section of Hematology Research at the Mayo Clinic in Rochester, Minneapolis. I have conducted research in the area of blood coagulation for over twenty years and have published numerous articles on blood coagulation and coagulation factors in pigs and humans.

2. I have reviewed the above-identified patent application, the Office Action mailed November 27, 1995 and the publications cited therein in connection with the above-identified application.

3. On page 3 of the Office Action mailed November 27, 1995, we see the precise and learned observations that the morphologic and histochemical attributes that the skin of

the pig and that of man are dissimilar, however, anybody who has every touched a pig and patted a baby's bottom already knew that. There are, however, considerable histochemical differences between my skin and that a black man. There are important immunochemical differences between my skin and that of my sister; and, even more enlightening, are the considerable morphologic and histochemical differences between the skin of my scalp and the skin on the soles of my feet. If Montagna was disappointed in the results obtained in his study of the pig, it was perhaps because he had erred in choosing the wrong model for studies relating to skin.

4. Bleeding, of course, is the phenomenon Dr. Comp required in his studies. Our studies have, for many years, focused on bleeding and coagulation in the pig. The porcine clotting system is not identical to the human clotting system. In our application of normal human clinical coagulation tests to the pig, we found differences in activities among the coagulation factors when compared to human, but all the pig factors worked to correct the deficiencies in the human test plasmas. This ability is, in effect, the foundation of using porcine factor VIII therapeutically in selected cases of hemophilia where it has proved to be a life-saving intervention. We have studied porcine factor VIII and have purified it using murine monoclonal antibodies, a strategy which was subsequently adapted in many laboratories to the purification of human factor VIII. The porcine factor VIII is activatable by human and porcine thrombin and human and porcine factor Xa and it is inactivated by human and porcine activated protein C. It contains APC-binding sequences on the light chain and an inactivating APC cleavage site between the A1 and A2 domains in concordance

with human factor VIII. It is stabilized through binding to von Willebrand factor as it is in the human. Human factor VIII binds to porcine and canine von Willebrand factor and porcine factor VIII levels are regulated in circulation by von Willebrand factor in a fashion similar to its regulation in humans. The hemostatic function of porcine platelets is inhibited by blockade of the same glycoprotein receptors, GPIb and GPIIb/IIIa, as are human platelets. Porcine blood is anticoagulated by chelation, by heparin/antithrombin III, and by hirudin at the same doses used for human. Accordingly, coagulation results obtained in pigs are predictive of results that would be obtained in humans.

5. While all primates are more closely related to man than the pig, the behavior of their clotting systems may be much more divergent. The blood of the Aotus monkey contains so much endogenous antithrombin III that serum cannot be reliably harvested from blood drawn into glass tubes, as it remains fluid for extended periods.

6. On the bottom of page 3, the Examiner communicates Chesebro's strategy of following animal studies with phase I and II clinical studies prior to phase III efficacy studies. This is not very illuminating because these are the strategies that have become common practice. But if ideas, applications, and reagents can't be protected prior to the initiation of human studies, there will be much less willingness to pursue new therapeutic modalities because of the cost, duration, and the generally public nature of human studies.

7. Waldmann is a researcher in oncology, who reveals his own personal and professional biases (not data), which have little or no applicability to Dr. Comp's application. By its nature cancer requires protracted treatment regimens and therapeutic success is most

often measured as an attenuation, regression, or remission. If we were to *prima facie* reject strategies which have failed to cure cancer, there would be little or no medicine or surgery. Antimetabolites, antihistamines, steroids, immunotherapy, radiation, amputation, cytokines, vitamins, prune pits, and incantations have all been on the short end of the stick when matched against malignancies of one sort or another. More importantly, the treatment Dr. Comp proposes is used in acute settings in the pre-operative period or in response to severe trauma. There is no.concern over blocking antibodies at least for the initial, and probably only, treatment a patient might receive. The Examiner's reference to the HAMA response is in a context which essentially impugns the normal human immune response to foreign protein, of which anti-idiotypes are a salient feature. This absurdity notwithstanding, the patient population Dr. Comp's treatment would encompass would primarily consist of single exposure opportunities.

8. The remaining discussion on page 5, I must admit, bewilders me. There seems to be a significant amount of weight put on the observation that, apparently, "only" one murine monoclonal antibody is approved for treatment of human disease. The Examiner clearly comes at this situation as a defect in this application. On "any given Sunday" this same state of affairs could be taken by an unbiased reviewer as an enabling characteristic - one which, in a single stroke, invalidates all the preceding poppycock about immunogenicity and ineffectiveness of murine monoclonal antibodies in the treatment of human disease. Indeed, while the stiff formalism of legalese is a strength in providing the unambiguous communication of ideas, it also requires a consistency of intent which is not present in the

Examiner's comment. See on page 5 the rejection of ONCOSCINT as a supporting example. "None of the claims of the instant invention read on the diagnosis of cancer. ONCOSCINT is not approved for the treatment of human disease. DIGIBIND is used for acute digoxin intoxication. None of the claims of the instant invention read on the method of treating acute toxicity related to digoxin." We now await the sentence which says "DIGIBIND is not approved for the treatment of human disease." Where is it - is it possible that a second murine monoclonal antibody is approved? More to the point, why is this an issue in Dr. Comp's application? What percentage of experiments with murine monoclonal antibody therapy need to be successful to permit the issuance of a patent? Animal monoclonal antibodies are useful in treating humans, and would not be expected to cause a problem in acute, typically single or few applications.

9. The discussion on obviousness would be more persuasive if it were correct. On page 14 and 15 the Examiner's incorrectly ascribes a thrombin inhibitory activity to APC. One has to wonder whether this represents a global misunderstanding of the sense of the proposal. It appears from Dr. Comp's animal studies that any reagent which augmented the production and/or longevity of endogenous thrombin in a controllable way would be useful in the treatment of microvascular bleeding. The blockade of antithrombin III/thrombin interaction or of antithrombin III glycosaminoglycan binding, antibodies to protein S and antibodies to protein C, whether suppressing the activation to activated protein C or the expression of activated protein C activity would accomplish augmentation of the endogenous clotting system. In addition, antibodies or peptides which block factor VIII and factor V

activated protein C binding sites or cleavage sites without exerting inhibition would also enhance endogenous procoagulant activity. In fact, systemic infusions of active site blocked activated protein C would likely give a transient enhancement of procoagulant activity. Active site blocked thrombin has been shown to displace active thrombin from thrombomodulin and it, or other thrombomodulin blocking antibodies or peptides, would be an alternative realization of Dr. Comp's invention.

10. In reading the office action, the only term which repeatedly surfaced in my mind was "arbitrary and capricious." The Examiner states more than once that murine monoclonal antibodies are rapidly cleared from human circulation and presumes this is a shortcoming of the proposal, whereas in this context rapid clearance of the inhibitor would provide a better opportunity to regulate and terminate the induced procoagulation state. We now have three full floors of our building and a warehouse to hold the scientific and biomedical publications of the past 75 years. One can find statements to support or refute virtually any scientific contention, including those dealing with the shape of our planet, but the Patent and Trademark Office quotes one expert who testifies that murine monoclonal antibodies will not be useful in human disease and quickly follows with the statement that there are others in phase III clinical trials and, thus, basically says that other respected scientists, experts, investors, and agencies hold quite the opposite view. Making illogical, irrelevant, and purely obstructionist arguments, obscures the validity of proper objections, if any exist. It is unfortunate that, as the world awaits porcine livers with HLA determinants on their cell membranes as transplant donors, and has accepted as common place porcine

heart valves for human implementation, and has lived through decades of diabetics treated with porcine insulin, and has depended upon various animal antitoxins and antivenoms for relief from the slings and arrows of outrageous fortune, the Patent and Trademark Office seeks the counsel of the paralytically conservative and chooses to bury its head in the sands of time. It is frightening to understand that the direction and strategies which will determine the health and competitiveness of the US biomedical community are contingent upon the unsupportable objections to reasonable ideas which are backed by experimental data and clinical experience.

11. It is my expert opinion that the application as filed and defined by the claims is enabling to one of ordinary skill in the art of coagulation. It is my further opinion that the method of treatment and composition is not obvious from the publications cited by the Examiner in the Office Action mailed November 27, 1996.

12. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date:_____

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Dr. David N. Fass